REMARKS

After entry of this amendment, claims 31-34, 36-52, 67-73 will be pending in the application. Claims 31 and 67 have been amended to more particularly point out and distinctly claim that which Applicant regards as the invention. The amendments are fully supported by the specification as originally filed and, as such no new matter has been added. Applicants respectfully request that the amendments and remarks made herein be entered into the record of the instant application.

THE CLAIMS ARE NOT ANTICIPATED

Claims 31 and 32 are rejected under 35 U.S.C. § 102(b) as anticipated by Gross *et al.* (U.S. Patent No. 5,848,991). The Examiner contends that Gross inherently anticipates the claimed invention. For reasons detailed below, these rejections are erroneous and should be withdrawn.

First, the Examiner continues to erroneously interpret Gross as disclosing the delivery of drugs to the intradermal compartment of a human subject's skin using a single needle with an outlet at a depth of 250 microns to 2 mm. There simply is no description in Gross of a single needle having an outlet at that depth, furthermore Gross is devoid of any teaching of the depth at which the outlet falls within the skin.

Second, the Examiner has erroneously concluded that practicing Gross would inherently result in a pharmacokinetic profile (PK) similar to subcutaneous injection, but with a higher C_{max} and AUC. The Examiner has ignored the evidence provided by way of the Pettis Declaration submitted with the previous Amendment, dated October 31, 2005. The Pettis Declaration provides that the mere injection of a drug into the intradermal compartment does *not inevitably* result in a higher Cmax and a shorted Tmax as required by the claims. The Examiner has taken the position that Applicant has not proven that following the teachings of Gross would not result in the claimed pK profile.

While there is absolutely no evidence that practicing Gross would inherently result in the claimed PK profile, assuming *arguendo* Gross were used to inject a drug into the intradermal space, an enhanced PK profile as compared to subcutaneous delivery would *not inevitably* result. Mere injection of a drug into the intradermal compartment does not inevitably result in an enhancement of any PK parameters, let alone a higher C_{max} and shorter T_{max} as compared to subcutaneous delivery. In this regard, the Examiner's attention is invited to the Supplemental Declaration by Dr. Ronald J. Pettis under 37 C.F.R. §1.132, submitted herein ("the Supplemental Pettis Declaration") which evidences that mere injection of a drug to the intradermal compartment does *not inevitably* result in an enhanced PK profile as compared to subcutaneous delivery. In the particular example reported in the Supplemental Declaration, the T_{max}, C_{max} and AUC attained via intradermal delivery of Almotriptan was not significantly different from the T_{max}, C_{max} and AUC attained via subcutaneous delivery (*see* Supplemental Pettis Decl., ¶ 8).

In order for a prior art reference to inherently anticipate the claimed invention, the method disclosed must *inevitably* result in the claimed invention, *i.e.*, the claimed PK profile must be achieved *each time and every time* the methods of Gross are practiced. *In re Oelrich*, 666 F.2d 578, 212 U.S.P.Q. 323 (C.C.P.A. 1981); *Continental Can Co. USA Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991); *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 34 U.S.P.Q. 2d 1565 (Fed. Cir. 1995). In other words, in order to establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *See,* M.P.E.P. Sec. No. 2112, IV citing to *In re Robertson* , 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). In this instance, the extrinsic evidence (*i.e.*, the Supplemental Pettis Declaration.) makes clear that the claim limitation which requires an enhanced PK profile as compared to subcutaneous delivery is

not necessarily present in the Gross reference. As demonstrated by the Supplemental Pettis Declaration merely depositing a substance into the intradermal compartment will not inevitably result in a PK profile having a higher C_{max} and shorter $T_{max,}$ as required by the claims. (*See* Supplemental Pettis Decl., ¶8). Since Gross would not *inevitably* lead to the PK profile claimed, inherent anticipation cannot be found, and the rejection should be withdrawn.

No where in Gross is there any recognition that intradermal delivery of a substance via a properly configured needle and the application of appropriate pressure results in any enhancement of PK parameters as compared to subcutaneous delivery. Thus, even if in some instance of practicing Gross an enhanced PK profile as compared to subcutaneous delivery were to result, such a result would be an unrecognized accident. "The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *See,* MPEP Sec. No. 2112, IV citing to *In re Robertson* , 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). An accidental or unwitting duplication of an invention cannot constitute an anticipation. *In re Marshall*, 198 U.S.P.Q. 344.

There is no evidence on this record that practicing the methods of Gross would inherently result in delivering a drug having the PK profile claimed. Moreover, the evidence provided herewith shows that the claimed PK profile would not inevitably result from practicing the prior art. In the event the Examiner disagrees, and to the extent that any rejection is based on facts within his personal knowledge, applicants request that the Examiner provide an affidavit pursuant to the provisions of 37 CFR § 1.104(d)(2).

1. THE CLAIMED INVENTION IS NOT OBVIOUS OVER GROSS IN VIEW OF PURI OR D'ANTONIO

Claims 33-52 are rejected under 35 U.S.C. §103(a) as obvious over Gross in view of Puri *et al.*, 2000, *Vaccine*, 18: 2600-12 ("Puri"), or U.S. Patent No. 6,056,716 to D'Antonio

("D'Antonio") and in further view of US Patent No. 3,814,097 to Ganderton *et al.* ("Ganderton"), and Autret et al., 1991, Therapie; 46:5-8 ("Autret").

The Examiner contends that to the extent Gross does not inherently achieve the claimed pharmacokinetic profile -- this missing element is supplied by Puri or D'Antonio. The obviousness rejection is based on the mistaken assertion that "Puri and D'Antonio disclose that intradermal injections give much greater C_{max} values than subcutaneous" (Office Action, p.4). The premise for this rejection is incorrect, and the rejection should be withdrawn.

The claimed methods relate to the delivery of a macromolecular or hydrophobic drug via bolus administration to the intradermal compartment via a needle with an outlet depth configured to achieve delivery of that substance in the intradermal compartment and with pharmacokinetic parameters similar to, but enhanced over subcutaneous delivery. There is nothing in the references combined to suggest the use of a needle with an outlet depth as specified by the claims, nor is there anything in the combination of references cited to suggest the use of a bolus delivery to achieve the enhanced PK parameters as claimed. In order to establish a *prima facie* case of obviousness, three criteria need be met: (1) there must be a suggestion or motivation to modify the reference or combine the teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claim limitations. *See*, the M.P.E.P. at Sect. 2143. In this instance, the *prima facie* case has not been made. First, for the reasons detailed below, the Examiner is inappropriately combining drug delivery and vaccine delivery art. One skilled in the art of drug delivery would not be motivated to attribute the teachings of vaccine art to drug delivery. Second, there is nothing in the art to suggest that the use of bolus delivery to the intradermal compartment will result in an enhanced PK profile as claimed. Third, the combination of

references cited fails to recite each of the claim limitations cited, *e.g.,* the use of a needle with an outlet depth as specified by the claims.

Puri, which deals with vaccine delivery (not drugs) is concerned with the body's immune response to the vaccine -- in other words, how much antibody the body makes in response to vaccination -- not systemic distribution profiles, and certainly not C_{max} levels of the administered vaccine. To illustrate the point, at pp. 2609 - 2610, Puri describes an enhanced *immune response* -- as measured by a higher antibody response -- not an enhanced C_{max} and AUC of the vaccine substance as the Examiner contends.

D'Antonio relates to jet injection of vaccines and other substances -- not the intradermal bolus delivery of macromolecular or hydrophobic drugs as claimed. Notably, at col. 29, line 3, D'Antonio expressly states that the entire discussion (of the D'Antonio patent) focused on *intramuscular injection.* The remainder of that paragraph discusses the possibility of administering vaccines -- *not drugs* -- into the dermis, so that less antigen could be used to generate "an increasingly rapid and effective pick-up by the immune system" (D'Antonio, col. 29, ll. 23-26).

Unlike drugs, the efficacy and potency of vaccines are not evaluated using PK studies. By contrast, the efficacy of vaccines is typically evaluated by measuring their ability to confer a protective immunity in the host. Methods for assaying potency of immunogenic compositions such as vaccines include serologic testing such as measurement of antibody titers induced against the particular antigen. For example in Puri, an ELISA assay was developed to quantify antibody levels (not the injected vaccines) in the sera of immunized mice. Similarly, D'Antonio makes reference, not to a PK profile, but rather to a more rapid and effective pickup by the immune system.

The Examiner has improperly attributed parameters and properties of the drug delivery art to the vaccine art. Pharmacokinetic studies are meaningless in the vaccine art as

practitioners in this field do not gauge the potency of the vaccine by its ability to be circulated systemically. In fact, as evidenced by the World Health Organization Guideline on Non-Clinical Evaluation of Vaccine, pharmacokinetic studies, *e.g.*, determining serum or tissue concentrations of the vaccine are normally not needed and in fact shed no light on the efficacy of the vaccine.

The Examiner relies on Ganderton for the purported teaching that multiple needle arrays result in facilitating the distribution of delivered drug to a patient. The Examiner posits that it would have been obvious to use the methods disclosed by Gross, Puri, and D'Antonio, to use the device of Ganderton.

The Examiner relies on Autret for the purported teaching that intradermal delivery of a hormone results in a pharmacokinetic profile similar to subcutaneous delivery. The Examiner posits that it would have been obvious to modify the methods disclosed by Gross, Puri, and D'Antonio, with hormone delivery disclosed by Autret, to achieve similar pharmacokinetic profiles via intradermal and subcutaneous delivery. As already described, the combination of Gross, Puri, and D'Antonio fails to satisfy the legal standard for an obviousness rejection, and Autret fails to cure the deficiency of such a combination.

Autret does not describe an intradermal delivery system which is the subject matter of the instant invention. As set out in the specification as filed (*see* ¶ [0007] of the instant specification), although Autret alleges intradermal delivery of calcitonin, the length of the needle and the angle at which the needle was used for drug administration would have resulted in either subcutaneous delivery or, at best, delivery into the reticular dermis where the substance would either be slowly absorbed or diffuse into the subcutaneous region, which would be the functional equivalent of subcutaneous administration and absorption. Thus, the method for hormone delivery taught in Autret results in subcutaneous delivery of the substance, which explains the similar pharmacokinetic profile between subcutaneous

administration and reported intradermal delivery, as opposed to the improved pharmacokinetic parameters required by the claimed invention.

Thus, skilled artisans concerned with drug administration via an intradermal delivery system, would not apply or combine the disclosure in Puri/D'Antonio and Ganderton and Autret with those in Gross. Moreover, the references must be viewed without the benefit of hindsight vision afforded by Applicants' claimed invention. *M.P.E.P. § 2141.* Absent a suggestion for the teaching that PK parameters can be altered and enhanced by intradermal injection relative to subcutaneous injection, the rejection cannot stand. Thus the rejections of claims 33-52 under 35 U.S.C. §103(a) should be withdrawn.

2. CONCLUSION

The Applicant respectfully requests that the Examiner enter the amendments and consider the remarks made herein. Withdrawal of all rejections, and an allowance is earnestly sought. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

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